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COMMENTARY

Protons for Oropharyngeal Cancer Have Not Yet Justified Their Promise

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Our colleagues had a tough job to do. Using patient-reported outcomes (PRO) instruments that may have lacked sensitivity to elicit subtle differences in outcomes important to patients, they compared PROs in oropharyngeal cancer patients treated with intensity modulated proton therapy (IMPT) versus those in patients treated with intensity modulated photon therapy (IMRT) (1). Sio et al hypothesized that because IMPT reduces the low-dose bath to the anterior oral cavity, brainstem, and posterior neck, IMPT could result in less symptom burden and better quality of life (QOL). In the end, this hypothesis was not clearly proven, in part owing to challenges such as a small sample size, treatment across different eras, variance in systemic therapies, and unequal follow-up. This research was developed in an environment in which their institution had invested a fortune in the IMPT, a pressure we must acknowledge. This article focused exclusively on the potential QOL benefits promised by the new technology.

We all appreciate the suffering the current standard of chemoradiation inflicts on our patients (2-4). However, when introducing a new modality into the cancer armamentarium, it would be optimal to introduce change within the context of the standard of care. Despite timely phase 3 data failing to show the effectiveness of induction chemotherapy in improving survival (5, 6), as the authors point out, 77% of the patients in the IMPT group received induction chemotherapy. This was a serious confounding variable, particularly in a QOL study. As has been discussed (7), induction chemotherapy in head and neck cancer patients can interfere with subsequent completion of curative therapy and could have put the IMPT group at a QOL disadvantage relative to IMRT. Personal communication assures us that the treatment volumes were not altered because of responses to induction chemotherapy (8).

Furthermore, the extent of disease of IMPT and IMRT patients was not well matched. To place the data in context, 74% of the IMPT patients were $p16^{+}$, and 89% only had T1/T2 disease, a most favorable cohort. Likewise, 42% of the IMPT patients had N0-2a disease. In the IMRT group the percentage of patients with T3/4 disease was tripled, and 74% of the patients had N2b-N3 disease. As might be expected in a group with a lower burden of primary disease, pretherapy swallowing and chewing were significantly better for the IMPT patients (mean scores 0.83 vs 1.87, $P = .041$), another confounding variable. It is unclear to what extent these stage and function variables reflected other fundamental baseline differences between the groups.

In any case, in these disparate groups, with the confounding variable of induction chemotherapy predominantly administered in the group with the most favorable disease, the goal was to compare PROs across 3 phases, designated as acute, subacute (<3 months after treatment completion), and chronic phases. The main outcomes data are found in Table 2 of the article. As is common with many QOL studies, the response rate declines after treatment, and only 18 of 35 IMPT patients and 28 of 46 IMRT

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patients provided long-term data. Of the "top 11" symptoms only taste (subacute) and appetite (subacute and chronic) in the posttreatment time period were significantly different, favoring IMPT, though the difference in average symptom scores was small, at 1-2 point differences. The composite score for the "top 11" was not clinically or statistically different for any time point, but the composite score for the "top 5" symptoms was different in the subacute time period.

Despite advantageous dosimetry and less disease to treat, there was little to justify proton therapy in either the acute or chronic phases of treatment. Unfortunately mucositis, pain, xerostomia, and dysphagia, the most important and ubiquitous toxicities oropharyngeal cancer patients experience, were similar between the 2 cohorts.

We acknowledge that patients do suffer in the interval from completion of radiation until we see them for that first follow-up visit, and the importance of PRO improvements in the subacute phase should not be underestimated. We must be careful not to over- or under-interpret the data presented. The limitations of this study may be masking an actual meaningful QOL benefit with IMPT—what the authors call a "signal." The relatively minor differences elicited in this study could be indicative of a larger or longer-term underlying effect that was not adequately captured by the MDASI-HN. In the face of a considerable investment in this technology, we appreciate the authors' decision to release data showing there were no significant PRO advantages documented for either the acute or chronic phases of patients' treatment.

Decades ago bone marrow transplant wards for breast cancer were nearly ubiquitous, and the specialists resisted a randomized trial (9). It was the health maintenance organizations and the insurance companies that forced medicine into conducting randomized trials, and thankfully most of the investigators acted ethically, and we came to know the truth. Our colleagues from the MD Anderson Cancer Center are advocating for randomized trials to test the utility of IMPT. This is commendable. We also agree on the need to develop robust, clinically meaningful endpoints that could serve to power such a study. We look for future randomized studies comparing IMPT with IMRT for patients with oropharyngeal cancer, with both groups receiving standard-of-care treatment, which today means concurrent therapy without induction chemotherapy.

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